REMARKS

Claims 1-38 are currently pending in the application; non-elected claims 10-23 and 27-32 are withdrawn from consideration pursuant to 37 C.F.R. 1.142(b). Claims 33-38 are canceled.

Applicant thanks the Examiner for the courtesy of a telephone interview on June 16, 2003, during which the Applicant's attorney and the Examiner discussed the rejection under 37 C.F.R. § 103. The essence of the interview is summarized below.

Rejection Under 35 U.S.C. § 103

Claims 1-9, 24-26, and 33-38 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Montminy (U.S. Pat. No. 6,063,583) in view of Gilman et al. (U.S. Pat. No. 6,306,649), for the reasons of record set forth in Paper No. 8, mailed July 2, 2002 (first Office Action). Applicant respectfully traverses this rejection.

For the reasons described below, Applicant respectfully submits that the Examiner has mischaracterized the teachings of the Gilman et al. reference, and failed to establish a *prima facie* case of obviousness under the requirements of 35 U.S.C. § 103(a). To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings (*In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)). Second, there must be a reasonable expectation of success. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicant's disclosure. Finally, the prior art reference (or references when combined) must teach or suggest *all the claim limitations*. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974).

Mischaracterization of the Gilman et al. reference

Montminy (the primary reference) teaches the use of three constructs to identify compounds that disrupt the formation of a complex between CREB and CBP. Specifically, Montminy teaches (1) a reporter construct which includes a GAL4 response element operatively

linked to a reporter gene; (2) a fusion protein which contains a GAL4 DNA binding protein operatively linked to the Kinase Inducible Domain (KID) of CREB; and (3) a fusion protein containing an activation domain operatively linked with the KIX binding domain of CBP. When the KIX domain of construct (3) binds to the phosphorylated CREB of construct (2), the GAL4 DNA binding protein then binds to the GAL4 response element of construct (1), which then induces the reporter gene. When a compound is added which disrupts the complex of CREB and CBP, the reporter gene is not activated.

In contrast to the transient, tripartite expression system disclosed in the Montminy reference, the instant invention relates to cell lines and kits, which contain a stably integrated recombinant nucleic acid construct having two elements. Specifically, the Applicant's construct comprising (1) a reporter gene operably linked to a recognition sequence for a sequence-specific DNA-binding protein, and (2) a fusion protein containing a sequence-specific DNA binding domain and a conditionally active transactivation domain. The sequence-specific DNA binding domain specifically binds to the recognition sequence, and the binding results in transactivation of the reporter gene

In the first Office Action (Paper No. 8), the Examiner acknowledges that Montminy does not specifically teach stable integration of the constructs into the cell, and relies upon the Gilman et al. reference to supply this deficiency. The Office Action portrays Gilman et al. as suggesting the stable integration of the Montminy system by characterizing the reference as follows:

> Gilman et al. teach an expression system comprising a nucleic acid encoding a fusion transcription factor protein comprising a DNA binding domain. . . and a heterologous transcriptional activation domain . . . . This reference teach[es] that constructs encoding the chimeric transcription factor and target gene construct can be introduced into cells as one or more DNA molecules, such as by a vector designed for integration into the host cell's chromosome (column 20). It also teaches that one may have a target site for homologous recombination where it is desired that a construct be integrated at a particular locus, such as for deletion and/or replacement of an endogenenous gene (columns 20-21). Reporter systems for assaying the fusion protein transcriptional activity in the cell are also taught which comprises a reporter gene such as luciferase, CAT, secreted alkaline phosphatase, etc., operatively linked to a binding site for the transcription factor (column 13). . . . (paragraph bridging pages 4 and 5).

Applicant respectfully submits that the Examiner has mischaracterized the reference. The Examiner recites two passages out of context, in an unsuccessful attempt to show that the Gilman et al. reference teaches stable integration of the "entire assay system taught by Montminy" (first Office Action, page 6, lines 3-6). However, neither passage cited by the Examiner supports this position. First, the Examiner cites a passage from column 20 of Gilman et al., which allegedly "*teaches* that constructs encoding the chimeric transcription factor and target gene construct can be introduced into cells . . . by *a vector designed for integration into the host cell's chromosome*." Rather than teaching stable integration, as the Examiner suggests, the cited passage states that these chimeric constructs "may be introduced into a host cell by **any convenient means**" (column 20, lines 45-46). The reference then provides a comprehensive list of well-known means for introducing nucleic acid constructs into host cells, including using vectors capable of episomal replication or integration into the host cells' chromosomes, as well as "by protoplast fusion, electroporation, biolistics, calcium phosphate transfection, lipfection, microinjection of DNA or the like" (column 20, lines 46-56). The reference further states that "[i]n some instances, one may have a target site for homologous recombination, where it is desired that a construct be integrated at a particular locus" (column 20, line 66, through column 21, line 1). See also column 3, lines 26-42, which provides a generic listing of conventional means for introducing DNA constructs into cells. Thus, rather that "teach" stable integration, the cited reference teaches that any conventional means for achieving heterologous gene expression - whether transient or stable - can be used to introduce the chimeric construct comprising a transcription factor and a target gene.

The Examiner continues to mischaracterize the teachings of the Gilman et al. reference by immediately following this first misstatement with a second out-of-context reference, this time to a reporter gene construct in column 13. The Examiner seems to be implying that the Gilman references teaches stable integration of a construct comprising a transcription factor and a reporter gene. However, the Examiner has failed to point out that the passage in column 13 relates to **transient expression** of a construct comprising a reporter gene and a binding site for the transcription factor using an **expression vector (plasmid)**. The purpose of using the reporter

gene is to determine the activity of the transcription factor, i.e., whether it is a positive or negative regulator of transcription.

Thus, the Examiner's statement that Gilman et al. teaches the stable integration of the "entire assay system taught by Montminy" is clearly in error.

Lack of motivation to combine Montminy and Gilman et al.

Neither Montminy nor Gilman et al. teach or suggest a cell line or kit comprising a stably integrated recombinant nucleic acid construct as recited in Applicant's claims. As discussed above, Montminy teach a three-part expression system, comprising: (1) a first construct comprising a GAL4 response element and a reporter gene; (2) a fusion protein comprising a GAL4 DNA binding protein and the KID domain of CREB; and (3) a fusion protein containing an activation domain and the KIX binding domain of CBP. It does not teach a cell line comprising a recombinant nucleic acid comprising (1) a reporter gene operably linked to a recognition sequence for a sequence-specific DNA-binding protein, and (2) a fusion protein containing a sequence-specific DNA binding domain, and a conditionally active transactivation domain, as claimed herein. Nor is there any suggestion in the cited references to combine their teachings to stably integrate a recombinant DNA construct into the cell line, as required by Applicant's claims.

Based on the above-discussed mischaracterizations of the Gilman et al. reference, the Examiner then concludes that:

> It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the host cell comprising the vectors encoding the fusion proteins taught by Montminy by using vectors which are able to integrate the nucleic acid encoding the fusion protein and reporter construct, introducing the integration vector into a host cell, and selecting for host cells which have the nucleic acid stably integrated because Gilman et al. teach that it is within the ordinary skill in the art to do so for the same type of expression systems.
>
> One would have been motivated to do so for the expected benefit of being able to integrate the construct at a particular locus as taught by Gilman et al., which is useful in making cell lines which have the entire assay system taught by Montminy, with a known number of copies of each component of the system,

> which gives one of ordinary skill better control and reproducibility of the system. Based upon the teachings of the cited reference and the ordinary skill in the art, there would have been a reasonable expectation of success in being able to integrate the expression system taught by Montminy stably into a cell as taught by Gilman et al. (Paper No. 8, page 5, last paragraph, and page 6, first paragraph).

As discussed above, the Gilman et al. reference fails to teach or suggest stable integration of chimeric constructs into a host cell, much less stable integration of a reporter gene construct. Instead, this reference teaches that **any** known method of introducing DNA constructs into cells, including the use of expression plasmids and various transfection techniques, will work. Moreover, there is no teaching or suggestion of integrating a reporter gene construct into the genome of a host cell or organism. In fact, such integration would **destroy the intended purpose or function** of the Gilman et al. invention, which is to provide methods and materials (recombinant DNA sequences and cells comprising these sequences) for achieving **high-level expression of a target gene** in genetically engineered cells, including genetically engineered cells within whole organisms. The only disclosed use of a reporter gene in the Gilman et al. reference is to test the activity of the transcription factor, which is then incorporated into a host cell. To stably integrate a reporter gene into these cells or organisms would serve no purpose, and would likely negatively impact the expression level of the target gene, as well as the function and viability of the modified cell. Because stably integrating a reporter gene into the Gilman cell would destroy the intended purpose or function of the cell, one of ordinary skill of art would not have been motivated to combine these two references to arrive at the claimed invention. See, e.g., *Ex parte Weber*, 154 U.S.P.Q. 491 (Pat. & Tr. Office Bd. App. 1967) ("to rearrange the machine of Hempel et al. as proposed by the examiner . . . would completely alter the construction and mode of operation of the [Hempel machine] so that it would not function in its intended manner." Thus, the "obviousness of the proposed changes is not derived from the cited prior art, but only from appellant's disclosure.")

Because the Gilman et al. reference does not stand for the proposition for which it was cited, it would not have been obvious to modify the Montminy reference as suggested by the Examiner.

Moreover, the mere fact that references can be combined does not render the resultant combination obvious unless the prior art also suggest the desirability of the combination. *Berghauser v. Dann, Comr. Pats.*, 204 U.S.P.Q. 393 (Dist. DC 1979); *ACS Hospital Systems, Inc. v. Montefiore Hospital*, 221 U.S.P.Q. 929 (Fed. Cir. 1984). Citing references which merely indicate that isolated elements and/or features recited in the claims are known is not a sufficient basis for concluding that the combination of claimed elements would have been obvious. *Ex parte Hiyamizu*, 10 U.S.P.Q.2d 1393 (Bd. Pat. App. & Inter. 1988).

Combination does not result in claimed invention

In addition to the lack of motivation to combine the references, even if combined, the teachings of Montminy and Gilman et al. do not result in the claimed invention. Neither Montminy nor Gilman et al. teach a stably integrated recombinant nucleic acid construct containing a report gene operably linked to a recognition sequence for a sequence-specific DNA-binding protein, and a sequence encoding a fusion protein, wherein the fusion protein comprises a sequence-specific binding domain and a conditionally active transactivation domain.

Applicants therefore respectfully submit that the Examiner has not established a *prima facie* case of obviousness over Montminy in view of Gilman et al..

Applicant therefore respectfully submits that the claims are not obvious in view of the cited references, and respectfully requests that the rejection on this basis be reconsidered and withdrawn.

Objection Under 37 C.F.R § 1.75

Claims 33-38 are objected to under 37 C.F.R. § 1.75 as being substantial duplicates of claims 25 and 26. Although not acquiescing to this rejection, Applicant has canceled claims 33-38 to expedite allowance of the application.

Double Patenting Rejections

Claims 1-9, 24-36, and 33-38 remain provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 and 24-32 of co-pending U.S. Serial No. 09/637,511 in view of Montminy (U.S. Pat. No. 6,063,583).

Upon the indication of allowable subject matter, Applicant will provide a Terminal Disclaimer limiting the term of any patent issuing from the present application to that of the patent issuing from U.S. Serial No. 09/637,511.

Applicant submits that in view of the foregoing remarks, all issues relevant to patentability raised in the Office Action have been addressed. Applicant respectfully requests the withdrawal of rejections over the claims of the present invention.

Respectfully submitted,

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